What is claimed is:

1. A method for determining a degree of toxicity or efficacy of an agent comprising;

exposing a tissue of interest in a subject to the agent such that the agent contacts said tissue of interest,

obtaining a biological sample containing protein from said tissue of interest,

measuring levels of protein markers of toxicity or efficacy in said sample, and

comparing the levels of said markers to the levels of the same markers in a control sample or other sample exposed to known toxic or known effective agents to determine whether the tissue of interest in a subject is experiencing toxicity or an effective response or the degree of such responses.

2. The method of claim 1 wherein the protein toxicity or efficacy markers are selected from the group consisting of the markers in Table 8.

3. The method of claim 2 wherein the protein toxicity or efficacy markers are selected from the group consisting of the markers in Table 9, alanine aminotransferase (MSN 204), and MSN 1255.

4. The method of claim 1 further comprising;

measuring levels of individual proteins in a proteome of said biological sample from the tissue of interest,

comparing these levels with levels of the same proteins in the proteome from a sample from a tissue of interest from a

control subject or a subject treated with one or more other agents known to be toxic or effective, and

detecting which proteins are increased or decreased by a statistically significant amount.

5. The method of claim 4 wherein the statistically significant amount is determined as a $p<0.01$.

6. The method of claim 5 wherein $p<0.001$.

7. The method of claim 1 wherein the agent is a pharmaceutical and it is given in a pharmaceutically appropriate amount.

8. The method of claim 1 wherein the agent is an antilipemic agent.

9. The method of claim 1 wherein the levels of protein markers determines the relative amount of toxicity or effectiveness.

10. The method of claim 1 wherein the levels of protein markers in the test biological sample is compared to the levels of the same protein markers in biological samples exposed to a known effective agent or known toxic agent.

11. The method of claim 4 wherein the levels of protein markers in the test biological sample is compared to the levels of the same protein markers in biological samples exposed to a known effective agent or known toxic agent.

12. The method of claim 4 wherein said proteome is prepared by two-dimensional electrophoresis.

13. The method of claim 1 wherein the comparing is to the control and the control is a biological sample contain protein from the same tissue of interest before the tissue of interest is exposed to the agent.

14. A protein toxicity or efficacy marker selected from the proteins of Table 8.

15. A protein toxicity or efficacy marker of claim 14 selected from the list in Table 9, alanine aminotransferase (MSN 204), and MSN 1255.

16. A binding reagent specific for a protein selected from the group consisting of protein toxicity or efficacy markers of claim 14 bound to a detectable label.

17. A binding reagent specific for a protein selected from the group consisting of protein toxicity or efficacy markers of claim 15.

18. A method of monitoring efficacy or toxicity in a subject exposed to an agent comprising;

measuring the quantity or level of one or more protein toxicity or efficacy marker of claim 14.

19. A method of monitoring efficacy or toxicity in a subject exposed to an agent comprising;

measuring the quantity or level of one or more protein toxicity or efficacy marker of claim 15.

20. A protein selected from the group consisting of proteins listed in Table 9, alanine aminotransferase (MSN 204), and MSN 1255.

21. A protein according to claim 20 in isolated form.

22. A binding reagent specific for the protein of claim 20.

23. The binding agent of claim 22 bound to a detectable label.

24. A method for screening candidate compounds for blood cholesterol regulating activity comprising;

contacting a candidate compound with a tissue of interest,

measuring the level of a protein marker of Table 8, and

comparing the level of protein marker to the level of protein marker in a control tissue of interest or a tissue of interest contacted with a known anti-cholesterol synthesis agent,

wherein said protein marker is not HMG-CoA synthase or HMG-CoA reductase.

25. The method according to claim 24 wherein said protein marker is isopentenyl-diphosphate delta-isomerase.

26. A pharmaceutical composition for reducing blood cholesterol levels comprising;

a modifier of the level of or the activity of a protein marker of Table 8, wherein said protein marker is not HMG-CoA synthase or HMG-CoA reductase, and

a pharmaceutically acceptable carrier,

wherein said modifier was identified by the process of claim 24.

27. A method for reducing blood cholesterol levels comprising administering the pharmaceutical composition of claim 26 to a cell producing said protein marker.

28. The method of claim 27 wherein the cell is in an intact animal.

29. The pharmaceutical composition of claim 26 wherein said protein marker is isopentenyl-diphosphate delta-isomerase.

30. A method for screening candidate compounds for blood cholesterol regulating activity comprising;

contacting a candidate compound with a protein marker of Table 8,

measuring the activity of said protein marker or the binding of said compound to said protein marker, and

selecting for further development those compounds which effect activity or bind,

wherein said protein marker is not HMG-CoA synthase or HMG-CoA reductase.

31. The method according to claim 30 wherein said protein marker is isopentenyl-diphosphate delta-isomerase.

32. A pharmaceutical composition for reducing blood cholesterol levels comprising;

a modifier of the synthesis of or the activity of a protein marker of Table 8, wherein said protein marker is not HMG-CoA synthase or HMG-CoA reductase, and

a pharmaceutically acceptable carrier,

wherein said modifier was identified by or produced by the process of claim 30.

33. A method of identifying biological pathways in a cell affected by the action of an agent, comprising;

a) obtaining at least two biological samples, one containing protein from a subject, tissue or cells exposed to said agent, and one containing protein from a subject, tissue or cells not exposed to said agent,

b) determining levels of proteins in the proteome from each biological sample,

c) comparing the levels of each protein in said proteomes,

d) determining which proteins have statistically significantly higher or lower levels in each sample,

e) identifying a plurality of the determined proteins, and

f) deducing which biological pathways are affected based on the identities of said proteins,

wherein said biological pathways contain at least one protein having a statistically significantly higher or lower level in a comparison between the two samples.

34. The method of 33 wherein one sample has a combination of two or more protein markers which have statistically significantly higher or lower levels than the same combination of protein markers in the other sample.

35. The method of claim 34 wherein the method is performed on at least three samples, one exposed to a known therapeutic amount or concentration, one exposed to a known toxic amount or concentration of the agent and one unexposed.

36. A standardized two-dimensional electrophoretic distribution of proteins from a biological sample from a subject or tissue of interest exposed to an antilipemic agent at a toxic amount or concentration.

37. A set of plural standardized two-dimensional electrophoretic distributions of proteins from biological samples from subjects or tissues of interest exposed to each of a plurality of pharmaceuticals wherein each pharmaceutical is indicated for the same condition.

38. A method for identifying a toxic response marker to an agent comprising:

contacting a first test animal or tissue of interest with a dosage of said agent known not to cause toxicity,

contacting a second test animal or tissue of interest with a dosage of said agent known to cause toxicity,

obtaining a biological sample from said first, second and control test animals or tissues of interest, where the control is not contacted with said agent,

measuring the level of each protein in a proteome in a biological sample from each test animal,

comparing the levels between test animals to determine statistically significant differences for each protein or combination of proteins,

wherein proteins with statistically significant differences between toxic and both non-toxic dosages and controls are toxicity markers.

39. A method for identifying a toxicity or efficacy marker for an agent according to claim 38 wherein the dosage of said agent known to not cause toxicity is an effective dose.

40. A protein toxicity marker identified by the method of claim 38.

41. A method of monitoring toxicity in a subject exposed to an agent comprising;

measuring the quantity or level of one or more toxicity markers determined by the method of claim 38.

42. A binding reagent specific for a protein toxicity marker of claim 40.

43. The binding reagent of claim 42 bound to a detectable label.

44. A method for evaluating the toxicity or efficacy of an antilipemic agent comprising;

determining the presence or level of at least one protein marker indicative of toxicity or efficacy in a biological sample from a subject receiving said antilipemic agent,

comparing the level to a standard level of said at least one marker,

wherein detection of an abnormal level of the at least one marker is indicative of toxicity or efficacy.

45. The method according to claim 44 wherein the protein marker is selected from the group consisting of protein markers of Table 8.

46. The method according to claim 44 wherein the protein marker is selected from the group consisting of protein markers of Table 9, alanine aminotransferase (MSN 204), and MSN 1255.

47. The method according to claim 44 wherein the proteome of the biological sample is measured.

48. A method for determining drug toxicity or efficacy susceptibility markers comprising,

obtaining biological samples from 1) individuals known to respond well to the drug and 2) individuals known to experience toxicity from the drug,

measuring levels of the protein markers for each biological sample,

detecting which toxicity or efficacy markers are increased or decreased above a statistically significant amount thereby determining toxicity or efficacy susceptibility markers.

49. A method for determining drug toxicity or efficacy susceptibility markers according to claim 48 further comprising,

measuring levels of individual proteins in the total proteome of each biological sample,

comparing these levels of proteins of the total proteome from one type of biological sample to another type,

wherein proteins that are increased or decreased above a statistically significant amount are thereby determined to be toxicity or efficacy susceptibility markers.

50. A method for determining whether an individual is susceptible to toxicity or effective activity from a drug comprising;

obtaining a biological sample from the individual,

measuring the levels of the toxicity or efficacy susceptibility markers of claim 49, and

comparing the level of each marker to previously determined standards from claim 49 to determine the individual's susceptibility to toxicity of the particular drug.

51. Protein susceptibility markers produced by the process of claim 48.

52. Protein susceptibility markers produced by the process of claim 49.

53. A binding reagent specific for a protein susceptibility markers of claim 51.

54. A binding reagent specific for a protein susceptibility markers of claim 52.

55. A method for determining whether a protein is a protein marker of efficacy or toxicity for an agent when the protein is not a statistically significant marker comprising;

a) determining protein markers for an agent of interest that have an altered level but with statistical significance less than an acceptable specified threshold by themselves,

b) repeating step a) with at least one related agent of interest,

c) comparing a list of protein markers from said agent of interest and a list from said related agent of interest,

wherein protein markers in common are considered protein markers for a group of related agents.

56. The method of claim 55 wherein said agent of interest and said related agent of interest are chemically related.

57. The method of claim 55 wherein said agent of interest and said related agent of interest have at least one common mechanism of action.

58. The method of claim 55 wherein said group of related agents are antilipemic agents.

59. The method of claim 55 wherein said related agent of interest is a drug used for comparable indications but functions by a different intended mechanism of action.

60. Protein markers produced by the method of claim 55.

61. A binding reagent specific for a protein marker of claim 60.

62. A method for determining whether a combination of proteins together form a protein marker of efficacy or toxicity

for an agent when the proteins individually are not markers with a desired level of statistical significance, comprising;

determining proteins which are at altered levels in biological samples from an animal treated with an agent of interest and control biological samples from an animal not treated with an agent of interest, which proteins are less than the desired level for statistically significant markers by themselves,

selecting two or more of said proteins,

combining the values for two or more of said proteins and determining whether the combination of values is altered in a statistically significant manner,

wherein said combination of proteins results in the desired level of statistically significant differences between biological samples from treated animals and biological samples from untreated animals.

63. The method of claim 62 wherein said agent of interest and said related agent of interest are chemically related.

64. The method of claim 62 wherein said agent of interest and said related agent of interest have at least one common mechanism of action.

65. The method of claim 62 wherein said group of related agents are antilipemic agents.

66. The method of claim 62 wherein said related agent of interest is a drug used for comparable indications but functions by a different intended mechanism of action.

67. A composition comprising the combination of proteins of claim 62 forming the protein marker.

68. A method for finding drug development targets for a known physiological activity comprising;

exposing a tissue of interest to an agent having a known physiological activity,

measuring the level of each protein in a proteome of a biological sample containing protein from said tissue of interest,

comparing the level of each protein to the level in a control biological sample,

determining which proteins are found in a statistically significant abnormal amount thereby indicating them to be protein markers, and

determining which of the protein markers is involved in the same metabolic pathway as said agent, thereby indicating these to be drug development targets.

69. Drug development targets determined by the method of claim 68.

70. A binding reagent specific for the drug development targets of claim 69.

71. The binding reagent of claim 70 bound to a detectable label.

72. The drug development targets of claim 69 selected from those of Table 8.

73. The drug development targets of claim 72 selected from those of Table 5.

74. A method for determining whether a protein is a protein marker of efficacy or toxicity for an agent when the protein is not a statistically significant marker comprising;

a) determining protein markers for an agent of interest and protein submarkers that have an altered level but are altered to less than a statistically significant amount by themselves,

b) comparing the level and direction of change of protein markers with the protein submarkers,

c) repeating steps a) and b) on a different biological sample from a different individual, and

d) comparing the protein submarker's altered level between different individuals,

wherein protein submarkers which are altered in tandem consistently with protein markers in level and direction or opposite direction are themselves considered protein markers.

75. Protein markers produced by the method of claim 74.

76. A binding reagent specific for a protein marker of claim 74.

77. A method for generating an index marker for a particular physiological state comprising;

determining protein markers which differ in a statistically significant manner between biological samples from an animal treated with an agent of interest and a control biological sample from an animal not treated with an agent of interest,

which proteins are statistically significant protein markers by themselves,

selecting two or more of said protein markers,

combining the values for two or more of said protein markers and determining whether the combination of values is altered in a manner of greater statistical significance.

78. An index marker determined by the process of claim 77.

79. An antisense compound capable of inhibiting expression of a gene listed in Table 8 but not Table 9.

80. A method for confirming protein markers or determining a metabolic pathway comprising;

contacting the tissue of interest with the antisense compound of claim 79, and

measuring a change in the levels of proteins in the proteome of the tissue of interest.

81. A method for determining whether plural pharmaceuticals act in an additive or synergistic manner comprising;

exposing a tissue of interest to a first pharmaceutical and obtaining a protein containing sample thereof,

exposing a tissue of interest to a first pharmaceutical and a second pharmaceutical and obtaining a protein containing sample thereof,

measuring the levels of protein markers in each sample,

comparing the changes in levels of protein markers between tissues of interest exposed to a first pharmaceutical and

tissues of interest exposed to a first and second pharmaceutical and

determining whether the effects of said first pharmaceutical and said second pharmaceutical is cumulative or synergistic.

82. A pharmaceutical composition comprising said first pharmaceutical and said second pharmaceutical when the effects are more than additive as determined by the method of claim 81.

83. A method for determining a reaction to an agent comprising;

exposing a tissue of interest in a subject to the agent such that the agent contacts said tissue of interest,

obtaining a biological sample containing protein from said tissue of interest,

measuring levels of protein markers of change in said sample, and

comparing the levels of said markers to the levels of said markers in biological samples from one or more of the following controls treated with an agent having the same efficacy mechanism of action, an agent having the opposite efficacy mechanism of action, an agent having an unrelated mechanism of action, an agent having having the same toxicity mechanism of action, an agent having the opposite toxicity mechanism of action, and an agent having an unrelated toxicity mechanism of action.

84. The method of claim 83 wherein the data for an agent having unrelated mechanisms of action is a composite agents

selected from a database of plural agents believed to have unrelated mechanisms of action.

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